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Clinical Features of COVID-19-Infected Patients With Elevated Liver Biochemistries: A Multicenter, Retrospective Study

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Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Hb, hemoglobin; hs-cTnI, high-sensitivity cardiac troponin I; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; WBC, white blood count.

Abstract

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) emerged in Wuhan, China. Although it has been reported that some COVID-19 patients showed elevated liver biochemistries, there are few studies regarding clinical features and prognosis of these patients. In this multicenter, retrospective study, we collected data on laboratory-confirmed COVID-19 patients from three hospitals in Wuhan, China, who died or were discharged between February 1, 2020, and February 20, 2020. The data on demographics, comorbidities, clinical symptoms, laboratory examinations on admission, complications, treatment, and outcome were collected. A total of 482 patients were enrolled in this study. Of those, 142 (29.5%) patients showed abnormal liver biochemistries on admission, and patients with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) accounted for 67.6%, 69.0%, and 16.2%, respectively. Those with abnormal liver biochemistries showed higher percentages of severe cases and comorbidities and were more likely to have dyspnea, chest distress or pain, and increased hemoglobin (Hb) on admission. Higher rates of complications and mortality and worse recovery when discharged were observed in patients with abnormal AST or TBIL. The multivariable regression analysis showed that chest distress or pain (odds ratio [OR], 1.765; $P = 0.018$), dyspnea (OR, 2.495; $P = 0.001$), elevated C-reactive protein [CRP] level (OR, 1.007; $P = 0.008$), elevated white blood count (WBC) (OR, 1.139; $P = 0.013$), and elevated Hb concentration (OR, 1.024; $P = 0.001$) were independent factors associated with elevated liver biochemistries in COVID-19 patients. *Conclusion:* Elevated liver biochemistries were common in COVID-19 patients. Patients with hypoxia or severe inflammation are more likely to experience increased liver biochemistries on admission. Those with abnormal AST or TBIL on admission are more likely to suffer from severe complications and death.

In December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak in Wuhan, China. The World Health Organization (WHO) named the disease coronavirus disease 2019 (COVID-19).[1] As of May 8, 2020, the cumulative number of infected people worldwide has risen sharply to more than 3.7 million with an alarming mortality rate of 6.9%.[(2)] The main clinical manifestations of COVID-19 include fever, cough, diarrhea, myalgia, and dyspnea. Although most patients show mild symptoms, some progress rapidly to critical conditions and develop acute respiratory distress syndrome (ARDS), acute respiratory failure, coagulopathy, septic shock, and even death.[(3)]

Retrospective studies have found that liver biochemical abnormalities occurred in some patients infected with COVID-19,[(4-6)] whereas a large-scale, multicenter study on the detailed manifestations and clinical features of these patients was absent. In this study, we aimed to analyze clinical characteristics and factors related to abnormal liver biochemistries in patients with COVID-19 to explore the value of these liver biochemical indexes.

Methods

Study design

In this multicenter, retrospective study, data on patients with laboratory-confirmed COVID-19 were collected from Wuhan Tongji Hospital, Union Hospital main district, and Jin Yin-tan Hospital (Wuhan, China) who died or were discharged between February 1, 2020, and February 20, 2020. Laboratory confirmation was defined as a positive result for the SARS-CoV-2 RNA on real-time reverse-transcription polymerase chain reaction (RT-PCR) assay of pharyngeal swab specimens. All patients enrolled received standard diagnosis and treatment based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (7th interim edition).

The study was approved by the Ethics Commission of Wuhan Tongji Hospital, Union Hospital, and Jin Yin-tan Hospital, and written informed consent was waived. To ensure the accuracy and completeness of the data, all authors reviewed the extracted data and revised errors immediately by checking the original case data after the errors were found.

Data collection

From the three hospitals, 484 patients who died or were discharged from February 1, 2020, to February 20, 2020, were included. After exclusion of 2 cases due to the large amount of missing data, a total of 482 cases were finally enrolled into analysis. Data on demographics, comorbidities (cardiovascular disease, chronic pulmonary disease, diabetes, malignancy, chronic liver disease, and chronic kidney disease), clinical symptoms (fever, rigor, cough, chest distress or pain, dyspnea, fatigue, myalgia, anorexia, and diarrhea), laboratory examinations (complete blood count, serum biochemical test, coagulation profile, renal and liver function, C-reactive protein [CRP], and lactate dehydrogenase [LDH]), imaging examination, complications, and treatment (antiviral agents, antibiotics, traditional Chinese medicine, corticosteroids, and mechanical ventilation) were collected from electronic medical records. In this study, liver biochemical abnormality was defined as any parameter more than the upper limit of normal value of alanine aminotransferase (ALT) (40 U/L), aspartate aminotransferase (AST) (40 U/L), and total bilirubin (TBIL) (21 μmol/L). All laboratory findings were the first laboratory test results on admission.

Statistical analysis

Continuous variables were described as medians and interquartile ranges (IQRs), and categorical variables were expressed as counts and percentages. We adopted independent *t* test or Mann-Whitney U test to analyze continuous variables based on normal-distributed data or nonnormal-distributed data. Categorical variables were compared with $\chi2$ test or Fisher's exact test. We divided patients into normal liver biochemistries group and abnormal liver biochemistries group to compare the differences of baseline characteristics, laboratory findings, and treatment between the two groups. To further analyze liver biochemical abnormality, the cases were divided into ALT normal group and ALT elevation group, AST normal group and AST elevation group, and TBIL normal group and TBIL elevation group. Univariate and multivariate logistic regression methods were used to investigate the factors associated with abnormal liver biochemistries on admission. Odds ratio (OR) was expressed with their 95% confidence intervals (CIs). All of the data were analyzed in SPSS version 22.0. Statistical tests were 2-tailed, and $P < 0.05$ was identified as statistically significant.

RESULTS

Clinical features

A total of 482 laboratory-confirmed COVID-19 patients were enrolled in this study (Table 1). The median age was 56.5 years (IQR, 39.0-67.3; range, 14-91 years), and 243 (50.4%) cases were male. Relevant laboratory results on admission were shown in Table 2. Of these patients, 142 (29.5%) had abnormal liver biochemistries on admission, and most of them were male (55.6%; $P = 0.139$) and older (median, 57.0; IQR, 42.8-67.0; $P = 0.413$). The proportion of severe patients in the abnormal liver biochemistries group was significantly higher than in the normal liver biochemistries group (52.8% vs. 33.2%; $P < 0.001$). The proportion of severe patients in the TBIL elevation group was the highest (69.6%; $P = 0.002$), followed by the AST elevation group (58.2%; $P < 0.001$), whereas the ALT elevation group was the lowest (47.9%; $P = 0.045$) (Table 3.1). The common comorbidities were hypertension (25.3%), chronic liver disease (19.9%), diabetes (14.9%), cardiovascular disease (7.7%), chronic obstructive pulmonary disease (COPD) (3.7%), malignancy (2.9%), and chronic kidney disease (1.2%). The proportion of patients with diabetes (22.5%; $P = 0.002$) and chronic liver disease (26.1%; $P = 0.029$) was higher in the abnormal liver biochemistries group. Chronic liver disease (96; 19.9%) included viral hepatitis (91; 18.9%) and nonalcoholic fatty liver disease (NAFLD) (5; 1%). Compared with the normal liver biochemistries group, the proportion of patients with viral hepatitis in the abnormal liver biochemistries group was significantly higher (24.6% vs. 16.5%; $P = 0.037$), and the proportion of patients with NAFLD was not significantly different between groups (2.1% vs. 0.6%; $P = 0.311$). Common symptoms included fever (88.0%), cough (60.0%), anorexia (40.0%), fatigue (33.0%), chest distress or pain (30.1%), and dyspnea (17.0%). Compared with the normal liver biochemistries group, the incidence of chest distress or pain (39.4%; $P = 0.004$) and dyspnea (28.9%; $P < 0.001$) was higher in the abnormal liver biochemistries group. The proportion of ARDS and acute cardiac injury in the AST elevation group and TBIL elevation group was significantly higher than in the normal liver biochemistries group (Table 3.1). In the abnormal liver biochemistries group, there were more patients who had received corticosteroid therapy (7.7%; P = 0.010) before admission, whereas the proportion of patients who had undergone antiviral therapy (55.6%; P = 0.021) was relatively smaller (Table 1). After admission, the proportion of patients who had received corticosteroid therapy was also higher in the abnormal liver biochemistries group (47.2% vs. 32.9%; P = 0.003) (Table 1).

Compared with normal liver biochemistries, patients with abnormal liver biochemistries had poor prognosis with a significantly higher proportion of death (29.6% vs. 6.5%; $P < 0.001$), especially in the AST elevation group (33.7% vs. 8.1%; $P < 0.001$) and TBIL elevation group (60.9% vs. 10.9%; $P < 0.001$) (Table 3.1). Among patients with abnormal liver biochemistries, the percentages of patients who had achieved chest computed tomography (CT) improvement (57.7% vs. 72.9%; P = 0.001), normal CRP (28.9% vs. 42.9%; P = 0.004), and normal lymphocyte count (59.9% vs. 74.4%; P = 0.001) were lower than in the normal group when discharged (Table 1).

Laboratory inspection

Compared with the normal liver biochemistries group, patients with abnormal liver biochemistries had higher levels of CRP, leukocytes, creatinine, LDH, D-dimer, hemoglobin (Hb), high-sensitivity cardiac troponin I (hs-cTnI), and globulin and lower levels of lymphocytes, eosinophils, and albumin (Table 2). The Hb of the abnormal liver biochemistries group (median, 132.5 g/L; IQR, 122.0-143.0) was higher than in the normal group (median, 127.0 g/L; IQR, 117.0-136.0) ($P < 0.001$), and the differences were statistically significant when grouped by ALT elevation (P = 0.001), AST elevation (P = 0.001), or TBIL elevation (P = 0.006). The levels of CRP and leukocytes in the liver biochemistries elevation groups were higher than in the normal groups ($P <$ 0.001). The absolute values of lymphocytes in patients with elevated AST ($P < 0.001$) and TBIL (P = 0.003) were lower, and the TBIL elevation group had the minimum lymphocyte count of 0.7×10^9/L (IQR, 0.4-1.1; P = 0.003) (Table 3.2). The levels of hs-cTnI were significantly higher in patients with elevated AST (10.7 vs. 3.6 pg/mL; $P < 0.001$) or TBIL (15.0 vs. 4.0 pg/mL; P = 0.002) than those with normal levels (Table 3.2).

Factors associated with elevated liver biochemistries

Multivariate logistic regression was performed to analyze the factors associated with elevated liver biochemistries (Table 4). It was found that chest distress or pain (OR, 1.765; 95% CI, 1.104-2.820; P = 0.018) , dyspnea (OR, 2.495; 95% CI, 1.434-4.341; P = 0.001), elevated CRP (OR, 1.007; 95% CI, 1.002-1.012; P = 0.008), increased white blood count (WBC) (OR, 1.139; 95% CI, 1.028-1.263; P = 0.013), and increased Hb (OR, 1.024; 95% CI, 1.009-1.039; P = 0.001) were independent factors associated with elevated liver biochemistries.

Discussion

In this multicenter, retrospective study, we found that elevated liver biochemistries were common in COVID-19 patients. Approximately one third of the subjects presented with elevated liver biochemistries on admission, which was similar with a previous report.[7] However, most of the patients just showed mild elevated liver biochemistries at the preliminary stage of infection,[8] which was consistent with what was found in our study that most patients only had slight elevation of ALT, AST, and TBIL on admission. The mechanism of abnormal liver biochemistries caused by SARS-COV-2 is still unclear. In our study, 19.9% of COVID-19 patients coexisted with chronic liver diseases (viral hepatitis and nonalcoholic fatty liver disease [NAFLD]). Viral hepatitis co-comorbidity accounted for a higher proportion in patients with elevated liver biochemistries (P = 0.037). However, it is hard to say whether NAFLD co-comorbidity contributes to elevated liver biochemistries because we only had 5 NAFLD patients. Although patients with previous liver diseases were easier to develop with abnormal liver biochemistries, it was possible that they had abnormal biochemistries before infected by SARS-CoV-2. Of the patients, 4.8% presented with elevated TBIL, especially direct bilirubin (DBIL), and median DBIL/TBIL was 0.42 (0.34-0.48). As reported by a recent study, angiotensin-converting enzyme 2 (ACE2) was highly expressed in type II alveolar epithelial cells as well as in bile duct cells and had an important role in mediating SARS-CoV-2 infection.[9] These findings indicated that elevated TBIL may be associated with SARS-CoV-2-induced bile duct cells injury rather than direct hepatic cells injury caused by the virus.[10,11]

We demonstrated that CRP and leukocyte count were associated with abnormal liver biochemistries, which was consistent with a previous study.[12] CRP, an acute phase protein, is an indicator for active inflammation. An increased number of leukocytes is a response to bacterial infection. Both are important clinical inflammatory indicators. It has been reported that the levels of CRP and WBC were significantly higher in severe cases,[13] and abnormal liver biochemistries were more commonly seen in critical patients.[6] In a previous COVID-19 study, patients who had been admitted to the intensive care unit (ICU) had higher levels of ALT and AST relative to non-ICU patients, and the proportion of patients with elevated AST was also higher in ICU patients (62% vs. 37%).[14] According to another study, 39.4% of severe patients showed elevated AST, whereas 28.1% had elevated ALT, the proportion of which were both higher than nonsevere cases.[15] Thus, patients with severe disease were more likely to have elevated liver biochemistries, which may be related to cytokine storm.[6] Cytokine storm is an overactive inflammatory response caused by pathogens, leading to a persistent activation of lymphocytes and macrophages that can secrete an abundance of inflammatory cytokines, followed by ARDS and multiorgan failure. Previous studies have shown that cytokine storm was associated with poor outcomes in SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) infection.[16,17] As reported, inflammatory cytokines reached the peak a few days after hospitalization, indicating that some cytokines might be involved in early stage of abnormal liver biochemistries.[18] It was also demonstrated in a study that more than half of the COVID-19 patients had elevated liver enzymes, which may be associated with drug effects or overreaction of the immune system [19]

In our study, 20 cases received glucocorticoids treatment before admission, including 17 severe patients. Based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*, glucocorticoids can be used in severe cases if necessary. The higher proportion of glucocorticoid therapy in patients with elevated liver biochemistries was possibly owing to the disease severity. Among the patients in this study, 63.5% received antiviral therapies before admission. Although more patients received antiviral treatments before admission in the normal liver biochemistries group, a report has demonstrated that the percentage of patients receiving lopinavir or ritonavir treatment after admission was markedly higher in patients with liver injury.[8] Accordingly, prospective studies are needed to investigate the exact association between various antiviral agents and liver function. In addition, in a previous study, the liver biopsy specimens showed moderate microvesicular steatosis and mild lobular and portal necrosis, which could be related to either SARS-CoV-2 infection or drug-induced liver injury.[20] Concrete evidence is still needed to confirm the cause of abnormal liver biochemistries.

In our study, increased Hb, chest distress or pain, and dyspnea were found to be associated with abnormal liver biochemistries. Hb is a functional protein in red blood cells that can deliver oxygen from the lungs to the far reaches of the body, and increased Hb level is an indicator of chronic hypoxia. Chest distress and dyspnea indicate that oxygenation of the lungs may be significantly damaged. Hypoxia can cause liver damage through a decrease in membrane potential, reducing the level of adenosine triphosphate (ATP), damaging sodium pump activity, and increasing membrane permeability.[21] Liver congestion or ischemia can also cause secondary liver function damage in clinic. These results illustrated that hypoxia probably was a cause of abnormal liver biochemistries in COVID-19 patients.

In patients with elevated AST or TBIL, the proportions of severe and deceased cases and patients with ARDS and acute cardiac injury were higher compared with those in ALT-elevated patients, whereas the lymphocyte count was relatively lower. Our results showed that hs-cTnI was much higher in patients with elevated AST or TBIL, indicating that those patients may have cardiac injury. A previous study found that 7.2% of COVID-19 patients had elevated hs-cTnI.[22] Another study showed that hs-cTnI was elevated in the early stage of COVID-19 and sharply increased with the deterioration of the disease.[5] Elevation of hs-cTnI was more common in severe cases, and more than half of the deceased patients showed elevated hs-cTnI during hospitalization. Several studies have demonstrated that cardiac injury was associated with poor prognosis.[6,15,23] Thus, our results suggested that elevated AST and TBIL may be an indicator for cardiac injury and were associated with poor prognosis. In addition, as shown in the results, patients with elevated AST or TBIL had worse chest CT images and lower rates for normalization of CRP and lymphocyte count. Lymphocyte count is an important predictor for disease severity, prognosis, and therapeutic response.[14,24] Therefore, patients with elevated AST or TBIL were more severe and had worse prognosis or recovery conditions, reminding us to pay close attention to these patients.

A previous study has demonstrated that LDH is the independent risk factor for poor outcomes (transfer to the ICU or in-hospital death) in SARS patients.[25] Owing to the poor specificity, LDH cannot represent the specific indicator for liver injury.[26] In our study, LDH level was higher in patients with elevated liver biochemistries. Whether a combination of LDH, AST, and TBIL can more accurately predict the outcomes of COVID-19 patients needs further investigation.

This study has some limitations. First, it was a retrospective study, and some cases had incomplete medical history, such as the detailed treatment before hospitalization. Liver function of those patients with coexisting chronic liver diseases before infection cannot be evaluated. Second, death cases may affect the evaluation of some indices, such as the length of hospital stay, and asymptomatic or mild patients were isolated at home, so we were unable to enroll these patients. Third, direct evidence of abnormal liver biochemistries caused by SARS-COV-2 is still uncovered, and the underlying mechanism needs to be further studied.

In conclusion, our study demonstrated that although abnormal liver biochemistries were common in COVID-19 patients, most of them just showed mild elevation, which may result from chronic hypoxia and excessive inflammation. Patients with elevated AST or TBIL on admission may have cardiac injury simultaneously and need more attention because they had worse prognosis.

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TABLE 1. Clinical Features, Treatment, and Prognosis of COVID-19 Patients on Admission

Indicators	Total (482)	Liver Biochemistries Normal (340, 70.5%)	Liver Biochemistries Abnormal (142, 29.5%)	*P* Value
Age, median (IQR), years	56.5 (39.0-67.3)	55.5 (38.0-68.0)	57.0 (42.8-67.0)	0.413
Sex				
Male	243 (50.4%)	164 (48.2%)	79 (55.6%)	0.139
Female	239 (49.6%)	176 (51.8%)	63 (44.4%)	
Severity				
Nonsevere	294 (61%)	227 (66.8%)	67 (47.2%)	<0.001
Severe	188 (39%)	113 (33.2%)	75 (52.8%)	
Comorbidities				
Hypertension	122 (25.3%)	80 (23.5%)	42 (29.6%)	0.164
Diabetes	72 (14.9%)	40 (11.8%)	32 (22.5%)	0.002
Cardiovascular disease	37 (7.7%)	23 (6.8%)	14 (9.9%)	0.245
COPD	18 (3.7%)	10 (2.9%)	8 (5.6%)	0.155
Malignancy	14 (2.9%)	9 (2.6%)	5 (3.5%)	0.823
Chronic liver disease	96 (19.9%)	59 (17.4%)	37 (26.1%)	0.029
Chronic kidney disease	6 (1.2%)	6 (1.8%)	0 (0%)	0.253
Signs and symptoms				

Fever	424 (88%)	293 (86.2%)	131 (92.3%)	0.062
Rigor	58 (12%)	42 (12.4%)	16 (11.3%)	0.738
Cough	289 (60%)	203 (59.7%)	86 (60.6%)	0.861
Chest distress or pain	145 (30.1%)	89 (26.2%)	56 (39.4%)	0.004
Dyspnea	82 (17%)	41 (12.1%)	41 (28.9%)	<0.001
Fatigue	159 (33%)	107 (31.5%)	52 (36.6%)	0.273
Myalgia	74 (15.4%)	53 (15.6%)	21 (14.8%)	0.824
Anorexia	193 (40%)	130 (38.2%)	63 (44.4%)	0.210
Diarrhea	129 (26.8%)	92 (27.1%)	37 (26.1%)	0.821
Complications				
ARDS	44 (9.1%)	13 (3.8%)	31 (21.8%)	<0.001
Acute kidney injury	47 (9.8%)	29 (8.5%)	18 (12.7%)	0.162
DIC	1 (0.2%)	1 (0.3%)	0 (0%)	1.000
Acute cardiac injury	7 (1.5%)	0 (0%)	7 (4.9%)	<0.001
Treatment before admission				
Antiviral	306 (63.5%)	227 (66.8%)	79 (55.6%)	0.021
Antibiotic	303 (62.9%)	220 (64.7%)	83 (58.5%)	0.195
Corticosteroid	20 (4.1%)	9 (2.6%)	11 (7.7%)	0.010
Traditional Chinese medicine	136 (28.2%)	97 (28.5%)	39 (27.5%)	0.813
Other	101 (21%)	71 (20.9%)	30 (21.1%)	0.952
Treatment after admission				

Antiviral	472 (97.9%)	338 (99.4%)	134 (94.4%)	0.001
Antibiotic	436 (90.5%)	306 (90%)	130 (91.5%)	0.598
Traditional Chinese medicine	254 (52.7%)	189 (55.6%)	65 (45.8%)	0.049
Corticosteroid	179 (37.1%)	112 (32.9%)	67 (47.2%)	0.003
Mechanical ventilation	66 (13.7%)	42 (12.4%)	24 (16.9%)	0.185
Clinical outcome				
Discharged	418 (86.7%)	318 (93.5%)	100 (70.4%)	<0.001
Died	64 (13.3%)	22 (6.5%)	42 (29.6%)	
Discharge status				
Chest CT improvement	330 (68.5%)	248 (72.9%)	82 (57.7%)	0.001
Chest CT normal or fibrosis	49 (10.2%)	39 (11.5%)	10 (7%)	0.142
C-reactive protein normal	187 (38.8%)	146 (42.9%)	41 (28.9%)	0.004
Lymphocyte count normal	338 (70.1%)	253 (74.4%)	85 (59.9%)	0.001
Hospital stays, median (IQR), days	13 (10-17)	13 (10-18)	12 (9-16)	0.005

Data are presented as numbers (%) unless otherwise indicated.

Other treatments before admission include anti-inflammatory drugs, hypoglycemic drugs, and antihypertensive drugs.

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computed tomography; DIC, diffuse intravascular coagulation; IQR, interquartile range.

TABLE 2. Laboratory Findings of COVID-19 Patients on Admission

Indicators	Total (482)	Liver Biochemistries: Normal (340, 70.5%)	Liver Biochemistries: Abnormal (142, 29.5%)	*P* Value
Blood routine				
White blood cell count, $\times10^9$ /L	5.2 (3.9-6.8)	4.9 (3.8-6.3)	6.1 (4.6-8.4)	<0.001
<4	130/481 (27%)	101/339 (29.8%)	29/142 (20.4%)	<0.001
>10	37/481 (7.7%)	12/339 (3.5%)	25/142 (17.6%)	
Lymphocyte count, $\times10^9$ /L	1.1 (0.7-1.5)	1.2 (0.8-1.5)	0.9 (0.6-1.4)	<0.001
<1.0	202/481 (42%)	124/339 (36.6%)	78/142 (54.9%)	<0.001
Eosinophils count, $\times10^9$ /L	0.02 (0.00-0.07)	0.03 (0.00-0.07)	0.01 (0.00-0.05)	0.001
<0.02	226/481 (47%)	143/339 (42.2%)	83/142 (58.5%)	0.001
Platelet count, $\times10^9$ /L	202.0 (149.0-265.0)	205.0 (152.0-259.0)	194.5 (140.5-287.3)	0.509
Hemoglobin, g/L	129.0 (118.0-138.0)	127.0 (117.0-136.0)	132.5 (122.0-143.0)	<0.001
Infection-related biomarkers				
C-reactive protein, mg/L	16.1 (3.4-51.5)	10.8 (1.7-39.8)	42.7 (10.1-96.8)	<0.001
>10	268/462 (58%)	165/326 (50.6%)	103/136 (75.7%)	<0.001
Blood biochemistry				
Albumin, g/L	36.4 (32.0-39.8)	37.2 (33.1-40.4)	33.8 (30.7-37.7)	<0.001

<35	199/482 (41.3%)	112/340 (32.9%)	87/142 (61.3%)	<0.001
Globulin, g/L	31.0 (27.7-34.5)	30.3 (26.8-34.0)	32.7 (29.1-36.2)	<0.001
Alkaline phosphatase, U/L	64.0 (53.0-78.3)	61.0 (50.0-73.0)	74.0 (61.0-98.3)	<0.001
γ-glutamate transpeptidase, U/L	26.0 (16.0-48.0)	21.0 (14.0-37.8)	54.0 (30.8-99.3)	<0.001
Lactate dehydrogenase, U/L	244.0 (193.0-331.0)	224.0 (183.5-280.0)	358.0 (260.5-503.0)	<0.001
>245	223/450 (49.6%)	120/321 (37.4%)	103/129 (79.8%)	<0.001
Creatinine, μmol/L	68.0 (56.9-83.1)	65.3 (54.5-80.6)	73.5 (61.8-88.3)	<0.001
>133	14/480 (2.9%)	7/338 (2.1%)	7/142 (4.9%)	0.161
hs-cTnI, pg/mL	4.2 (1.9-11.3)	3.6 (1.1-7.6)	7.0 (2.2-20.2)	<0.001
Coagulation function				
Prothrombin time, seconds	13.4 (12.7-14.1)	13.4 (12.7-14.0)	13.6 (12.4-14.5)	0.152
≥16	24/458 (5.2%)	9/322 (2.8%)	15/136 (11%)	<0.001
D-dimer, μg/mL	0.6 (0.3-1.3)	0.5 (0.3-1.0)	0.9 (0.5-2.3)	<0.001
≥0.5	245/446 (54.9%)	143/313 (45.7%)	102/133 (76.7%)	<0.001

Data are n/N (%) and median (interquartile range [IQR]).

Abbreviations: COVID-19, coronavirus disease 2019; hs-cTnI, high-sensitivity cardiac troponin I.

TABLE 3.1. Clinical Features, Treatment, and Prognosis of COVID-19 Patients on Admission

Indicators	Total (482)	ALT ≤ 40 (386, 80.1%)	ALT > 40 (96, 19.9%)	*P* Value	AST ≤ 40 (384, 79.7%)	AST > 40 (98, 20.3%)	*P* Value	TBIL ≤ 21 (459, 95.2%)	TBIL > 21 (23, 4.8%)	*P* Value
Age, median (IQR), years	56.5 (39.0-67.3)	56.0 (39.0-68.0)	57.0 (40.3-66.8)	0.906	55.5 (38.0-68.0)	57.0 (47.8-67.0)	0.208	57.0 (39.0-68.0)	54.0 (44.0-63.0)	0.690
Sex										
Male	243 (50.4%)	190 (49.2%)	53 (55.2%)	0.294	187 (48.7%)	56 (57.1%)	0.136	231 (50.3%)	12 (52.2%)	0.863
Female	239 (49.6%)	196 (50.8%)	43 (44.8%)		197 (51.3%)	42 (42.9%)		228 (49.7%)	11 (47.8%)	
Severity										
Nonsevere	294 (61%)	244 (63.2%)	50 (52.1%)	0.045	253 (65.9%)	41 (41.8%)	<0.001	287 (62.5%)	7 (30.4%)	0.002
Severe	188 (39%)	142 (36.8%)	46 (47.9%)		131 (34.1%)	57 (58.2%)		172 (37.5%)	16 (69.6%)	
Comorbidities										
Hypertension	122 (25.3%)	101 (26.2%)	21 (21.9%)	0.387	92 (24%)	30 (30.6%)	0.176	114 (24.8%)	8 (34.8%)	0.284
Diabetes	72 (14.9%)	49 (12.7%)	23 (24%)	0.006	50 (13%)	22 (22.4%)	0.019	68 (14.8%)	4 (17.4%)	0.969
Cardiovascular disease	37 (7.7%)	29 (7.5%)	8 (8.3%)	0.787	28 (7.3%)	9 (9.2%)	0.530	35 (7.6%)	2 (8.7%)	1.000
COPD	18 (3.7%)	13 (3.4%)	5 (5.2%)	0.582	14 (3.6%)	4 (4.1%)	1.000	16 (3.5%)	2 (8.7%)	0.470
Malignancy	14 (2.9%)	11 (2.8%)	3 (3.1%)	1.000	10 (2.6%)	4 (4.1%)	0.660	14 (3.1%)	0 (0%)	1.000
Chronic liver disease	96 (19.9%)	69 (17.9%)	27 (28.1%)	0.024	69 (18%)	27 (27.6%)	0.034	92 (20%)	4 (17.4%)	0.965

Chronic kidney disease	6 (1.2%)	6 (1.6%)	0 (0%)	0.475	6 (1.6%)	0 (0%)	0.462	6 (1.3%)	0 (0%)	1.000
Signs and symptoms										
Fever	424 (88%)	336 (87%)	88 (91.7%)	0.213	331 (86.2%)	93 (94.9%)	0.018	405 (88.2%)	19 (82.6%)	0.631
Rigor	58 (12%)	46 (11.9%)	12 (12.5%)	0.875	49 (12.8%)	9 (9.2%)	0.331	55 (12%)	3 (13%)	1.000
Cough	289 (60%)	225 (58.3%)	64 (66.7%)	0.134	230 (59.9%)	59 (60.2%)	0.956	274 (59.7%)	15 (65.2%)	0.757
Chest distress or pain	145 (30.1%)	105 (27.2%)	40 (41.7%)	0.006	108 (28.1%)	37 (37.8%)	0.064	136 (29.6%)	9 (39.1%)	0.332
Dyspnea	82 (17%)	53 (13.7%)	29 (30.2%)	<0.001	53 (13.8%)	29 (29.6%)	<0.001	75 (16.3%)	7 (30.4%)	0.141
Fatigue	159 (33%)	119 (30.8%)	40 (41.7%)	0.043	122 (31.8%)	37 (37.8%)	0.261	156 (34%)	3 (13%)	0.037
Myalgia	74 (15.4%)	58 (15%)	16 (16.7%)	0.690	61 (15.9%)	13 (13.3%)	0.521	71 (15.5%)	3 (13%)	0.985
Anorexia	193 (40%)	151 (39.1%)	42 (43.8%)	0.407	148 (38.5%)	45 (45.9%)	0.183	187 (40.7%)	6 (26.1%)	0.162
Diarrhea	129 (26.8%)	101 (26.2%)	28 (29.2%)	0.552	103 (26.8%)	26 (26.5%)	0.953	126 (27.5%)	3 (13%)	0.128
Complications										
ARDS	44 (9.1%)	33 (8.5%)	11 (11.5%)	0.376	19 (4.9%)	25 (25.5%)	<0.001	34 (7.4%)	10 (43.5%)	<0.001
Acute kidney injury	47 (9.8%)	36 (9.3%)	11 (11.5%)	0.529	36 (9.4%)	11 (11.2%)	0.582	45 (9.8%)	2 (8.7%)	1.000
DIC	1 (0.2%)	1 (0.3%)	0 (0%)	1.000	1 (0.3%)	0 (0%)	1.000	1 (0.2%)	0 (0%)	1.000
Acute cardiac injury	7 (1.5%)	4 (1%)	3 (3.1%)	0.292	2 (0.5%)	5 (5.1%)	0.004	5 (1.1%)	2 (8.7%)	0.037
Treatment after admission										
Antiviral	472 (97.9%)	380 (98.4%)	92 (95.8%)	0.227	379 (98.7%)	93 (94.9%)	0.050	453 (98.7%)	19 (82.6%)	<0.001
Antibiotic	436 (90.5%)	346 (89.6%)	90 (93.8%)	0.220	345 (89.8%)	91 (92.9%)	0.365	416 (90.6%)	20 (87%)	0.824
Traditional Chinese medicine	254 (52.7%)	204 (52.8%)	50 (52.1%)	0.893	214 (55.7%)	40 (40.8%)	0.008	247 (53.8%)	7 (30.4%)	0.028
Corticosteroid	179 (37.1%)	137 (35.5%)	42 (43.8%)	0.134	127 (33.1%)	52 (53.1%)	<0.001	167 (36.4%)	12 (52.2%)	0.126

Mechanical ventilation	66 (13.7%)	50 (13%)	16 (16.7%)	0.344	49 (12.8%)	17 (17.3%)	0.238	60 (13.1%)	6 (26.1%)	0.144
Clinical outcome										
Discharged	418 (86.7%)	339 (87.8%)	79 (82.3%)	0.153	353 (91.9%)	65 (66.3%)	<0.001	409 (89.1%)	9 (39.1%)	<0.001
Died	64 (13.3%)	47 (12.2%)	17 (17.7%)		31 (8.1%)	33 (33.7%)		50 (10.9%)	14 (60.9%)	
Discharge status										
Chest CT improvement	330 (68.5%)	265 (68.7%)	65 (67.7%)	0.859	276 (71.9%)	54 (55.1%)	0.001	323 (70.4%)	7 (30.4%)	<0.001
Chest CT normal or fibrosis	49 (10.2%)	42 (10.9%)	7 (7.3%)	0.298	43 (11.2%)	6 (6.1%)	0.138	48 (10.5%)	1 (4.3%)	0.553
C-reactive protein normal	187 (38.8%)	156 (40.4%)	31 (32.3%)	0.144	165 (43%)	22 (22.4%)	<0.001	181 (39.4%)	6 (26.1%)	0.200
Lymphocyte count normal	338 (70.1%)	272 (70.5%)	66 (68.8%)	0.742	282 (73.4%)	56 (57.1%)	0.002	332 (72.3%)	6 (26.1%)	<0.001
Hospital stays, median (IQR%), days	13 (10-17)	13 (10-18)	13 (11-16)	0.368	13 (10-18)	13 (9-16)	0.095	13 (10-17)	9 (4-13)	<0.001

Data are presented as numbers (%) unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DIC, diffuse intravascular coagulation; IQR, interquartile range; TBIL, total bilirubin.

TABLE 3.2. Laboratory Findings of COVID-19 Patients on Admission

Indicators	Total (482)	ALT: ALT ≤ 40 (386, 80.1%)	ALT: ALT > 40 (96, 19.9%)	*P* Value	AST: AST ≤ 40 (384, 79.7%)	AST: AST > 40 (98, 20.3%)	*P* Value	TBIL: TBIL ≤ 21 (459, 95.2%)	TBIL: TBIL > 21 (23, 4.8%)	*P* Value
Blood routine										
White blood cell count, $\times 10^9$ /L	5.2 (3.9-6.8)	5.0 (3.8-6.6)	6.1 (4.8-7.4)	<0.001	5.0 (3.8-6.5)	6.2 (4.5-8.1)	<0.001	5.1 (3.9-6.7)	10.6 (5.6-15.3)	<0.001
<4	130/481 (27%)	113/385 (29.4%)	17/96 (17.7%)	0.020	109/383 (28.5%)	21/98 (21.4%)	<0.001	126/458 (27.5%)	4/23 (17.4%)	<0.001
>10	37/481 (7.7%)	25/385 (6.5%)	12/96 (12.5%)		20/383 (5.2%)	17/98 (17.3%)		25/458 (5.5%)	12/23 (52.2%)	
Lymphocyte count, $\times 10^9$ /L	1.1 (0.7-1.5)	1.1 (0.7-1.5)	1.0 (0.7-1.5)	0.247	1.2 (0.8-1.5)	0.9 (0.6-1.2)	<0.001	1.1 (0.8-1.5)	0.7 (0.4-1.1)	0.003
<1.0	202/481 (42%)	155/385 (40.3%)	47/96 (49%)	0.122	142/383 (37.1%)	60/98 (61.2%)	<0.001	185/458 (40.4%)	17/23 (73.9%)	0.001
Eosinophils count, $\times 10^9$ /L	0.02 (0.00-0.07)	0.02 (0.00-0.07)	0.02 (0.00-0.07)	0.788	0.03 (0.00-0.07)	0.00 (0.00-0.04)	<0.001	0.02 (0.00-0.07)	0.01 (0.00-0.02)	0.008
<0.02	226/481 (47%)	182/385 (47.3%)	44/96 (45.8%)	0.800	162/383 (42.3%)	64/98 (65.3%)	<0.001	209/458 (45.6%)	17/23 (73.9%)	0.008
Platelet count, $\times 10^9$ /L	202 (149-265)	197.0 (148.5-256.0)	217.0 (152.5-313.8)	0.056	206 (152-265)	176.5 (132.3-269.5)	0.064	205 (152-268)	147 (87-202)	<0.001
Hemoglobin, g/L	129 (118-138)	128 (117-136)	133.0 (123.5-143.0)	0.001	128 (117-136)	133 (122-144)	0.001	128 (118-137)	140 (125-144)	0.006
Infection-related biomarkers										
C-reactive protein, mg/L	16.1 (3.4-51.5)	13.0 (2.4-45.8)	36.8 (7.1-81.5)	<0.001	10.2 (1.9-40.5)	57.1 (29.0-114.4)	<0.001	14.6 (3.0-47.6)	62.7 (24.8-137.7)	<0.001

>10	268/462 (58%)	203/371 (54.7%)	65/91 (71.4%)	0.004	185/367 (50.4%)	83/95 (87.4%)	<0.001	250/440 (56.8%)	18/22 (81.8%)	0.020
Blood biochemistry										
Albumin, g/L	36.4 (32.0-39.8)	37.0 (33.0-40.2)	33.5 (30.5-37.8)	<0.001	37.2 (33.1-40.3)	33.0 (30.6-36.2)	<0.001	36.5 (32.1-39.9)	34.0 (30.1-38.9)	0.094
<35	199/482 (41.3%)	141/386 (36.5%)	58/96 (60.4%)	<0.001	129/384 (33.6%)	70/98 (71.4%)	<0.001	186/459 (40.5%)	13/23 (56.5%)	0.128
Globulin, g/L	31.0 (27.7-34.5)	30.7 (27.1-34.4)	32.0 (28.6-35.6)	0.031	30.3 (26.9-34.0)	33.8 (29.8-36.7)	<0.001	30.6 (27.5-34.4)	34.4 (31.9-36.4)	0.004
Alanine aminotransferase, U/L	21.5 (15.0-35.3)	19.0 (14.0-26.0)	66.5 (51.0-88.5)	<0.001	NA	NA	NA	21.0 (15.0-34.0)	25.0 (18.0-57.0)	0.305
>40	96/482 (19.9%)	NA	NA	NA	NA	NA	NA	88/459 (19.2%)	8/23 (34.8%)	0.118
Aspartate aminotransferase, U/L	26 (19-37)	NA	NA	NA	23 (18-30)	59.0 (46.8-76.5)	<0.001	19 (26-36)	40 (24-87)	0.013
>40	98/482 (20.3%)	NA	NA	NA	NA	NA	NA	87/459 (19%)	11/23 (47.8%)	0.002
Alkaline phosphatase, U/L	64.0 (53.0-78.3)	61 (51-74)	77.5 (63.3-104.0)	<0.001	62 (51-76)	72.5 (60.0-96.3)	<0.001	63 (52-77)	87 (70-156)	<0.001
γ-glutamate transpeptidase, U/L	26 (16-48)	22.0 (15.0-35.3)	66.0 (38.3-122.5)	<0.001	22 (15-37)	56.0 (32.8-106.0)	<0.001	26 (16-45)	57 (22-123)	0.005
Lactate dehydrogenase, U/L	244 (193-331)	231.5 (186.0-303.3)	335.0 (256.8-454.0)	<0.001	229 (184-287)	405 (314-523)	<0.001	241.0 (192.5-319.5)	558.0 (231.5-829.5)	<0.001
>245	223/450 (49.6%)	152/362 (42%)	71/88 (80.7%)	<0.001	141/359 (39.3%)	82/91 (90.1%)	<0.001	208/429 (48.5%)	15/21 (71.4%)	0.040
Total bilirubin, μmol/L	9.1 (6.7-12.5)	8.8 (6.4-11.8)	10.7 (8.0-14.5)	<0.001	8.7 (6.4-11.6)	11.4 (8.0-14.9)	<0.001	8.9 (6.6-11.8)	22.9 (21.8-29.8)	<0.001

Direct bilirubin, μmol/L	3.6 (2.6-5.0)	3.5 (2.5-4.7)	4.4 (3.2-5.8)	<0.001	3.5 (2.5-4.5)	4.9 (3.4-7.0)	<0.001	NA	NA	NA
Direct bilirubin/ total bilirubin	0.42 (0.34-0.48)	0.41 (0.34-0.48)	0.44 (0.35-0.50)	0.063	0.40 (0.34-0.46)	0.48 (0.39-0.54)	<0.001	NA	NA	NA
Creatinine, μmol/L	68.0 (56.9-83.1)	67.0 (56.0-83.1)	70.1 (60.0-83.2)	0.349	66 (55-80)	78.9 (64.0-95.0)	<0.001	68.0 (56.1-82.9)	80 (64-100)	0.040
>133	14/480 (2.9%)	12/384 (3.1%)	2/96 (2.1%)	0.839	7/382 (1.8%)	7/98 (7.1%)	0.014	13/457 (2.8%)	1/23 (4.3%)	0.502
hs-cTnI, pg/mL	4.2 (1.9-11.3)	4.0 (1.8-10.3)	4.5 (1.9-15.5)	0.351	3.6 (1.2-7.9)	10.7 (2.9-21.8)	<0.001	4.0 (1.8-9.8)	15.0 (2.1-229.5)	0.002
Coagulation function										
Prothrombin time, seconds	13.4 (12.7-14.1)	13.5 (12.8-14.1)	13.3 (11.9-14.2)	0.493	13.3 (12.7-14.1)	13.8 (12.8-14.5)	0.036	13.4 (12.7-14.1)	14.7 (13.6-17.3)	<0.001
≥16	24/458 (5.2%)	16/366 (4.4%)	8/92 (8.7%)	0.161	14/363 (3.9%)	10/95 (10.5%)	0.019	18/436 (4.1%)	6/22 (27.3%)	<0.001
D-dimer, μg/mL	0.6 (0.3-1.3)	0.5 (0.3-1.2)	0.9 (0.5-1.7)	<0.001	0.5 (0.3-1.1)	1.0 (0.6-2.2)	<0.001	0.6 (0.3-1.2)	10.8 (1.1-38.6)	<0.001
≥0.5	245/446 (54.9%)	180/356 (50.6%)	65/90 (72.2%)	<0.001	168/353 (47.6%)	77/93 (82.8%)	0.001	228/425 (53.6%)	17/21 (81%)	0.014

Data are n/N (%) and median (IQR).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; hs-cTnI, high-sensitivity cardiac troponin I; NA, not available; TBIL, total bilirubin.

TABLE 4. Univariate and Multivariate Analysis of COVID-19 Patients With Abnormal Liver Biochemistries

Indicators	Univariate Analysis OR (95%CI)	*P* Value	Multivariate Analysis OR (95%CI)	*P* Value
Baseline characteristics				
Age, years	1.019 (1.006-1.032)	0.003	1.002 (0.986-1.019)	0.810
Sex, male	1.346 (0.908-1.995)	0.139	NA	NA
Severity				
Severe	2.249 (1.508-3.352)	<0.001	1.003 (0.595-1.691)	0.990
Comorbidities				
Hypertension	1.365 (0.880-2.117)	0.165	NA	NA
Diabetes	2.182 (1.305-3.647)	0.003	1.322 (0.717-2.441)	0.371
Cardiovascular disease	1.507 (0.752-3.022)	0.247	NA	NA
COPD	1.970 (0.761-5.100)	0.162	NA	NA
Malignancy	1.342 (0.442-4.078)	0.604	NA	NA
Chronic liver disease	1.678 (1.051-2.680)	0.030	1.478 (0.859-2.543)	0.158
Signs and symptoms				
Fever	1.910 (0.960-3.801)	0.065	NA	NA
Rigor	0.901 (0.488-1.662)	0.739	NA	NA
Cough	1.036 (0.695-1.547)	0.861	NA	NA

Chest distress or pain	1.836 (1.213-2.779)	0.004	1.765 (1.104-2.820)	0.018
Dyspnea	2.960 (1.817-4.823)	<0.001	2.495 (1.434-4.341)	0.001
Fatigue	1.258 (0.834-1.898)	0.274	NA	NA
Myalgia	0.940 (0.543-1.626)	0.824	NA	NA
Anorexia	1.288 (0.866-1.916)	0.211	NA	NA
Diarrhea	0.950 (0.609-1.482)	0.821	NA	NA
Treatment before admission				
Antiviral	0.624 (0.418-0.932)	0.021	0.685 (0.432-1.087)	0.108
Antibiotic	0.767 (0.514-1.146)	0.196	NA	NA
Corticosteroid	3.088 (1.251-7.625)	0.014	2.095 (0.724-6.062)	0.172
Traditional Chinese medicine	0.949 (0.613-1.469)	0.813	NA	NA
Other	1.015 (0.628-1.641)	0.952	NA	NA
Laboratory findings				
C-reactive protein, mg/L	1.013 (1.008-1.017)	<0.001	1.007 (1.002-1.012)	0.008
White blood cell count, $\times 10^9$ /L	1.248 (1.159-1.344)	<0.001	1.139 (1.028-1.263)	0.013
Platelet count, $\times 10^9$ /L	1.000 (0.998-1.002)	0.782	NA	NA
Lymphocyte count, $\times 10^9$ /L	0.546 (0.372-0.803)	0.002	0.937 (0.576-1.526)	0.795
Eosinophils count, $\times 10^9$ /L	0.083 (0.003-2.064)	0.129	NA	NA

Creatinine, μmol/L	1.004 (0.999-1.010)	0.100	NA	NA
Prothrombin time, seconds	1.018 (0.979-1.058)	0.364	NA	NA
D-dimer, μg/mL	1.050 (1.025-1.077)	<0.001	0.999 (0.964-1.035)	0.949
Hemoglobin, g/L	1.022 (1.009-1.035)	0.001	1.024 (1.009-1.039)	0.001
Globulin, g/L	1.102 (1.058-1.147)	<0.001	1.028 (0.979-1.079)	0.272
hs-cTnI, pg/mL	1.000 (1.000-1.000)	0.173	NA	NA

Other treatments before admission include anti-inflammatory drugs, hypoglycemic drugs, and antihypertensive drugs.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; hs-cTnI, high-sensitivity cardiac troponin I; NA, not available; OR, odds ratio.